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Health and Environmental Effects Profile for 1,1'-Biphenyl

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16. ABSTRACT

The Health and Environmental Effects Profile for 1,1'-biphenyl was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 1,1'-Biphenyl has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for 1,1'-biphenyl is 5×10^{-2} (mg/kg bw/day) for oral exposure.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 1,1'-BIPHENYL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	3
3.	EXPOSURE	7
4.	COMPOUND DISPOSITION AND PHARMACOKINETICS	9
4.1.	ABSORPTION	9
4.2.	DISTRIBUTION	9
4.3.	METABOLISM	10
4.4.	EXCRETION	11
5.	EFFECTS	13
5.1.	CARCINOGENICITY	13
5.2.	MUTAGENICITY	13
5.3.	TERATOGENICITY	16
5.4.	OTHER REPRODUCTIVE EFFECTS	16
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	17
5.6.	OTHER RELEVANT INFORMATION	19
6.	AQUATIC TOXICITY	21
6.1.	ACUTE TOXICITY	21
6.2.	CHRONIC EFFECTS	21
6.3.	PLANT EFFECTS	21
6.4.	RESIDUES	21
6.5.	OTHER RELEVANT INFORMATION	22
7.	EXISTING GUIDELINES AND STANDARDS	23
7.1.	HUMAN	23
7.2.	AQUATIC	23
8.	RISK ASSESSMENT	24
9.	REFERENCES	25
APPENDIX:	LITERATURE SEARCHED	37

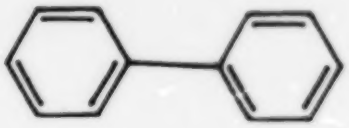
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

1,1'-Biphenyl is also known as biphenyl, diphenyl, bibenzene and phenylbenzene; its structure is given below:



Molecular formula: $(C_6H_5)_2$

Molecular weight: 154.2

The Chemical Abstract Services (CAS) Registry Number for this compound is 92-52-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Biphenyl is a colorless solid that crystallizes in the form of scales, and has a pleasant odor (Hawley, 1977). Some of its physical properties are given below (Weaver et al., 1979, unless otherwise stated):

Melting point:	69.2°C
Boiling point:	255.2°C
Flash point:	113°C
Specific gravity at 20°C:	1.041
Solubility in water at 25°C:	7.5 mg/ℓ (Verschueren, 1977)
Vapor pressure at 25°C:	0.01 mm Hg (Mackay et al., 1982)
Henry's law const. at 25°C:	4.08×10^{-4} m^3 atm. $mole^{-1}$ (Mackay et al., 1979)
Log Octanol/water partition coefficient:	3.16-4.17 (Hansch and Leo, 1981)

1.3. PRODUCTION DATA

Biphenyl was produced in 1982 by the following companies (SRI, 1983):

Bethlehem Steel	Sparrows Point, MD
Chemol	Greensboro, NC
Dow	Freeport, TX
Millmaster Onyx	Dalton, GA
Monsanto	Anniston, AL
Sybron	Wellsford, SC

Production volumes were not stated; however, Weaver et al. (1979) it was estimated that ~88 million pounds (40,000 metric tons) of biphenyl were produced in 1976.

Biphenyl can be produced by thermal dehydrogenation of benzene. This has been accomplished by passing benzene through a red hot iron tube or by bubbling benzene through molten lead or pumice, or by passing benzene over vanadium compounds at elevated temperatures (Weaver et al., 1979). Today, the main source of biphenyl is as a by-product of hydrodealkylation of toluene to form benzene. About 1 kg biphenyl is obtained for each 100 kg of benzene produced (Weaver et al., 1979).

1.4. USE DATA

Biphenyl has been used in organic synthesis, heat transfer fluids, dye carriers, food preservatives, as a starting product for polychlorinated biphenyl and as a fungistat for citrus fruits (Hawley, 1977; Weaver et al., 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Few data are available regarding the fate and transport of biphenyl in air. It can potentially enter the atmosphere as fume during its use as heat transfer fluid, and to a lesser degree, by volatilization from soil and water. The fate of biphenyl in air depends on its reactions with O_3, NO_x and free radicals (e.g., RO•, O•, RO_2• and OH•) and photolysis. No information is available regarding the reaction between biphenyl and other molecules in the atmosphere, but some data are available regarding its photolysis in laboratory tests. Freitag et al. (1982) reported that biphenyl underwent photodecomposition in a microphoto reactor using a wavelength above 290 nm. About 80 ppb of ^{14}C labeled biphenyl on silica gel was irradiated for 17 hours with an air current of 1.7 ℓ/hr. About 9.5% $^{14}CO_2$ and <0.1% organic fragments were collected as photodecomposition products.

Fukui et al. (1980) reported considerable photoreaction of biphenyl (impregnated into paper) in the presence of NO_x and UV radiation (>300 nm). A half-life of ~2 hours was observed for biphenyl. Both 2-nitrobiphenyl and 4-nitrobiphenyl were identified as reaction products.

A major aquatic source of environmental biphenyl contamination is the wastewater effluent of textile mills using the compound as a dye carrier (Weaver et al., 1979). It can also enter the environment from industrial processes and leaking heat exchangers that employ the compound. The fate of biphenyl in water and sediment depends on its reactivity with free radicals present in aquatic media, and its ability to undergo photochemical and microbial reactions. No information regarding chemical degradation was located. Most of the investigations have been focused on its biological degradation by bacteria, yeast and algae. Metabolism of biphenyl by aquatic

microorganisms appears to involve aromatic hydroxylation, with the production of 2-, 3- and 4-hydroxybiphenyl (Reichardt et al., 1981; Cerniglia et al., 1980) with further hydroxylation to 2,3-dihydroxybiphenyl (Treccani, 1974). A microbial metabolic pathway involving first ring fission and formation of benzoic acid and a 2-keto-4-hydroxypentanoic acid has been proposed (Ahmed and Focht, 1973; Treccani, 1974).

The photolysis of biphenyl in solution has been investigated by Kondo (1978) and Suzuki et al. (1982). Kondo (1978) reported that biphenyl underwent 50% degradation in ~40 hours under irradiation from a germicidal UV lamp (with UV spectra around 250 nm). Suzuki et al. (1982) reported the absence of mutagenic products from the photochemical reaction of biphenyls in aqueous sodium nitrate solution when the UV source was filtered to remove wavelengths <300 nm.

The transport of biphenyl in water involves its volatilization, dissolution and sorption to suspended particles. Lyman et al. (1982) estimated a 4.3 hour evaporative half-life of biphenyl from a flowing (1 meter/second) stream of water 1 meter deep, with an air current of 3 meters/second. Kilzer et al. (1979) measured the loss of radioactivity from an aqueous solution of 50 ppb ^{14}C biphenyl and observed loss of 3.45% of applied radioactivity per mL of evaporated water in 2 hours. Assuming an average water evaporation rate of 1.2 mL/hr (Kilzer et al., 1979), ~8% of biphenyl was lost in 2 hours.

No direct data were available regarding sorption of the compound to particulate matter, but substantial sorption may be predicted from the log octanol/water partition coefficient of >4 (Banerjee et al., 1980; Mackay et al., 1980; Swann et al., 1983). This prediction is in agreement with the experimental data of Freitag et al. (1982) that showed 50% of the biphenyl

applied to activated sludge in water (1 g dry sludge/ℓ of water) remained as nonextractable residue.

The bioaccumulation of biphenyl in aquatic organisms has been investigated. The algae, Chlorella fusca and Leuciscus idus melanotus, were reported to have experimental bioaccumulation factors of 540 and 282, respectively, in a static test system (Geyer et al., 1981; Freitag et al., 1982). A bioaccumulation factor of 436 and an uptake rate constant of 6.8 for rainbow trout were reported by Neely (1979). Sabljic and Protic (1982) have predicted a bioaccumulation factor of 340 based on the relationship between molecular connectivity indices and estimates of bioaccumulation factors for other chemicals. These factors are relatively low, so one can predict that biphenyl may not be strongly bioaccumulated in the environment. There has been some concern that chlorination of recycled water containing biphenyl may result in the production of chlorinated biphenyls (Gaffney, 1974), which are known to be stable in the environment.

The fate and transport of biphenyl in soil has been investigated. Biphenyl may not significantly volatilize from soil as evidenced by the study of Kilzer et al. (1979). Radiolabeled (^{14}C) biphenyl (50 ppb) was incorporated into wet sand, loam and humus. The authors observed that ~1.7, 1.0 and 0.1% respectively, of the applied radioactivity had evaporated in 2 hours.

Degradation of biphenyl by soil microorganisms may contribute significantly to the disposition of biphenyl in the environment. Degradation of biphenyl has been observed to occur in Saccharomyces cerevisiae, with the formation of benzoic acid (Karenlampi and Hynninen, 1981). Bacterial degradation of biphenyl has been reported by Smith and Rosazza (1974) in Streptomyces sp.; Ahmed and Focht (1973) in Achromobucter; Treccani (1974) and

Catelani et al. (1970) in Pseudomonas putida; Cerniglia et al. (1980) in Oscillatoria sp.; Lunt and Evans (1970) in gram negative bacteria; Tsuchi et al. (1977) in Acaligenes sp. 559; and Furukawa et al. (1978) in Acaligenes Y42 and Acinetobacter P6. Bacteria generally oxidize biphenyl to 2,3-dihydroxybiphenyl by way of cytochrome P-450 systems.

Biodegradation of biphenyl by fungi has been reported by many investigators, including Dodge (1981), Smith and Rosazza (1974) and Smith et al. (1980, 1981). Fungi seem to metabolize biphenyl in a manner similar to mammalian systems, with the production of 4-hydroxy- or 2-hydroxybiphenyl and 4,4'-dihydroxybiphenyl.

Biphenyl is degraded by activated sludge as reported by Korte and Klein (1982) and Freitag et al. (1979, 1982), who observed 9.1% conversion to CO_2 in 2 days.

Leaching of biphenyl through soil may not occur to a great extent because of its high octanol/water partition coefficient and low water solubility. If soil microbes metabolize biphenyl to the more polar hydroxy biphenyls and dihydroxy biphenyls, however, leaching of these metabolites into groundwater may occur.

3. EXPOSURE

Paper impregnated with biphenyl has been used in citrus packing to reduce fruit damage by fungus during shipment and storage. Many investigators have detected biphenyl in fruit packed with biphenyl impregnated paper. The conditions leading to optimization of fungicidal effect with minimum biphenyl residue were reported by Nagy and Wardowski (1981). Residual biphenyl levels are associated with a number of variables including the condition of the fruit (washed vs. unwashed, waxed vs. unwaxed), the temperature of storage and the number of impregnated pads used. Nagy and Wardowski (1981) have reported a range of 10-85 µg biphenyl/kg whole fruit in tangerines exposed under various conditions. Florida grapefruits shipped to Japan were determined to contain 0-150 mg biphenyl/kg peel or whole fruit (Wardowski et al., 1979). Isshiki et al. (1982) reported levels of biphenyl in the edible portions of grapefruit, oranges and lemons to be 0.02-123, 0-0.012 and 0.02-0.12 mg/kg, respectively.

Krstulovic et al. (1977) reported airborne concentrations of biphenyl (3.2-250 pg/m³) from diesel exhaust.

The U.S. EPA STORET data base contains monitoring data for biphenyl from eight sites. A concentration of 2 µg/ℓ was found in the Tennessee River, and sediment levels ranged from 5000 mg/kg in a roadside ditch in Kentucky to 4 µg/kg in Lake Michigan at the mouth of the Galien River. Effluent from industrial and water treatment facilities was found to contain 0-130 µg/ℓ of biphenyl. Williams et al. (1982) measured biphenyl concentrations in Great Lakes Municipal drinking water and reported a concentration range of 0.3-31.9 ng/ℓ. Biphenyl has been detected at 1-5 ng/ℓ in Athens, Georgia, drinking water (Thruston, 1978).

Stuermer et al. (1982) measured the biphenyl concentration in three coal seam aquifers previously shown to have high organic contamination. This area had been the site of an underground coal gasification process that had been inactive for 15 months. Groundwater samples were found to contain 25-43 µg/ℓ of biphenyl.

4. COMPOUND DISPOSITION AND PHARMACOKINETICS

4.1. ABSORPTION

Specific data regarding the uptake and absorption of biphenyl were not encountered in the available literature. The absorption of biphenyl has been demonstrated in a variety of species by the detection of urinary and biliary metabolites after oral administration of the compound. Rabbits, guinea pigs and pigs given biphenyl by gavage in either soya oil or propylene glycol excreted at least 20% of the dose in the urine 24 hours after treatment (Meyer, 1977; Meyer et al., 1976a). Rats given an oral dose of ^{14}C-biphenyl excreted 75-80% of the dose in 24 hours (Meyer et al., 1976a).

Absorption of biphenyl in rabbits upon dermal administration and in rats, mice and rabbits upon inhalation exposure was demonstrated by Deichmann et al. (1947). When a solution of biphenyl in olive oil was repeatedly applied to the depilated backs of rabbits, alterations in spleen morphology were observed in several animals. Repeated inhalation exposure to biphenyl-impregnated celite dust (0.005-0.3 mg/ℓ) caused hepatic and renal effects in rabbits, rats and mice. These distant toxic effects indicate that biphenyl had been absorbed by these routes of administration.

4.2. DISTRIBUTION

Meyer et al. (1976a) administered ^{14}C-biphenyl orally to rats and determined the disposition of the compound up to 96 hours after dosing. About 85, 0.1 and 0.6% of the total administered radioactivity was found in the urine, in the expired air as $^{14}CO_2$, and in the tissues, respectively.

Meyer and Scheline (1976) found 12 biphenyl metabolites in the bile collected for 96 hours after biphenyl administration by gavage to rats. These metabolites accounted for 5.2% of the administered dose.

Once absorbed, biphenyl is translocated to the liver by the circulatory system. In the liver, biphenyl is hydroxylated and conjugated, thus making it more polar. Most of an orally administered dose of biphenyl appears in the urine, but some may appear in the bile and in the feces.

4.3. METABOLISM

The *in vivo* and *in vitro* metabolism of biphenyl has been studied extensively. The first metabolic study of biphenyl was conducted in 1891 by Klingenberg, who demonstrated that 4-hydroxybiphenyl was a metabolite in dogs. Since this initial experiment, many authors have reported similar hydroxylation of biphenyl in a variety of species. Better analytical techniques have allowed the identification of other and more extensively hydroxylated metabolites. By derivatizing urinary metabolites and analyzing them with gas chromatography, Meyer and Scheline (1976), Meyer (1977) and Meyer et al. (1976a,b) have identified over 10 mono-, di- and tri-hydroxybiphenyl metabolites in the urine of rats, pigs, guinea pigs and rabbits. These metabolites have been found as mercapturic acid conjugates (West, 1940) and as glucuronide conjugates (Millburn et al., 1967). A major metabolite in the rat, mouse, guinea pig, rabbit and pig was reported to be 4-hydroxybiphenyl (Meyer, 1977; Meyer and Scheline, 1976; Parke, 1968). 4,4'Dihydroxybiphenyl has also been identified as a major metabolite in the pig (Meyer et al., 1976b) and the rat (Meyer and Scheline, 1976). 2'-Hydroxybiphenyl was a significant metabolite of biphenyl in the mouse (Parke, 1968). Wiebkin et al. (1976) reported that isolated rat hepatocytes metabolized biphenyl primarily to 4-hydroxybiphenyl, and also to 4,4'-hydroxybiphenyl, both of which were then conjugated. A small amount of 2-hydroxybiphenyl was produced. When 4-hydroxybiphenyl was incubated with the hepatocytes, it was hydroxylated to 4,4'-dihydroxybiphenyl. Bianco et al.

(1979) reported that rat hepatic microsomes metabolize biphenyl to the 4-, 2- and 3-hydroxybiphenyl which are conjugated to form glucuronides and sulfates. The 4-hydroxybiphenyl isomer was the major metabolite.

That biphenyl metabolism is mediated by a cytochrome P-450 system was suggested by Burke and Bridges (1975), and evidence of an arene oxide intermediate, which may result in binding to biomacromolecules was reported by Bridges et al. (1979) and Halpaap et al. (1977). Support for the P-450 metabolism of biphenyl was provided by Halpaap-Wood et al. (1981), who reported that greater amounts of hydroxybiphenyls were obtained in in vitro assays, using liver homogenates, when rats were first treated with 3-methylcholanthrene or Aroclor 1254, which are known P-450 inducers.

4.4. EXCRETION

Biphenyl is primarily excreted in the urine as mercapturic acids or glucuronides following hydroxylation and conjugation. Fecal excretion is of less importance, but several investigators have identified biphenyl metabolites in bile.

Meyer et al. (1976a) administered ^{14}C-biphenyl by gavage to rats and monitored their urine, feces and expired air for up to 96 hours after administration. About 85, 7 and 0.1% of the radioactivity was excreted in the urine, feces and expired air, respectively. Radioactivity in the lung, heart, kidney, brain, spleen, liver, skeletal muscles, peritoneal fat, genitals and gastrointestinal tract accounted for 0.6% of the administered dose after 96 hours. Metabolites in the urine were found to be of two types, phenolic and acidic. Meyer and Scheline (1976) further characterized the phenolic urinary metabolites of biphenyl in the rat by preparing derivatives followed by analysis with gas chromatography/mass spectrometry. Approximately 30 and 25% of the administered label was present in the urine as

phenolic (conjugated) and acidic metabolites, respectively, after 96 hours. Fecal excretion accounted for 4.7% and biliary excretion accounted for 5.2% of the administered dose during the 24 hours after administration. The metabolites of orally administered biphenyl in the pig, guinea pig and rabbit are found primarily in the urine of these animals, although the guinea pig excreted 20% of the dose in the feces (Meyer et al., 1976b; Meyer, 1977). Over two-thirds of this fecal excretion consisted of unchanged biphenyl. These studies demonstrate that biphenyl absorption or metabolism may differ depending on the species.

5. EFFECTS

5.1. CARCINOGENICITY

Biphenyl was among 130 pesticides evaluated for carcinogenicity in B6AKF1 and B6C3F1 mice by oral and subcutaneous administration (BRL, 1968). Groups of 18 male and 18 female 28-day-old mice of each strain were given a single subcutaneous injection of 46.4 mg biphenyl dissolved in DMSO per kg of body weight, followed by observation for 18 months. Similar groups of 7-day-old mice were given daily gavage doses of 215 mg biphenyl/kg in gelatin until age 28 days, and then given a diet containing 517 ppm of biphenyl for the next 18 months. Positive, negative and vehicle controls were included in the study. Animals were weighed every 6 months, and their lymphatic and pulmonary systems, livers, skin, mammary glands and uteri were subjected to histopathological examination at the termination of the exposure period. No increased incidences of tumors were found for any group or method of administration when compared with controls (BRL, 1968).

Ambrose et al. (1960) conducted a chronic feeding study in rats and examined the animals for tumors after treatment. Groups of 15 male and 15 female albino rats were given diets containing 0, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5 or 1.0% biphenyl for 700 days. Following treatment, a histopathological examination was conducted on the breast, hypophysis, adrenals, uteri, lungs, bladder and other tissues. Several malignant and benign tumors were found in treated and control rats, but their occurrence was not related to biphenyl administration.

5.2. MUTAGENICITY

Several authors have reported the results of microbial and cell culture tests to assess the genotoxic potential of biphenyl (Table 5-1). All assays have failed to demonstrate any mutagenic activity of biphenyl, except for

TABLE 5-1

Summary of Mutagenicity Testing of Biphenyl

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1538, TA98, TA100	plate incorporation	4-2500 µg/plate	± rat liver S-9	--	NC	Anderson and Styles, 1978
Reverse mutation	S. typhimurium G-46, TA1535, TA100, C3076, TA1537, D3052, TA1538, TA98	plate incorporation (gradient)	0.1-1000 µg/mL	± rat liver S-9	--	NC	Cline and McMahon, 1977
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	plate incorporation	≤10 mg/plate	±	--	NC	Waters et al., 1982
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	plate incorporation	"up to toxic concentrations"	+	--	NC	Bronzetti et al., 1981
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	1-100 µg/plate	±	--	NC	Hirayama et al., 1981
Reverse mutation	Escherichia coli WP2, WP2 urvA⁻	plate incorporation (gradient)	0.1-1000 µg/mL	± rat liver S-9	--	NC	Cline and McMahon, 1977
Reverse mutation	E. coli WP2 uvrA'	plate incorporation	≤10 mg/plate	±	--	NC	Waters et al., 1982
DNA damage	E. coli WP2, WP2 uvrA, CM571, WP100	disc	4000 µg/disc	-	--	growth inhibition was compared between wild type and DNA repair deficient strains	Hirayama et al., 1981

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Chromosomal aberration	Chinese hamster fibroblast and cell line	cell culture	60 µg/l	--	--	NC	Ishidate and Odashima, 1977
Unscheduled DNA synthesis	isolated rat hepatocytes	cell culture	10^{-6} to 10^{-8} M	--	--	NC	Brouns et al., 1979
Unscheduled DNA synthesis	isolated rat hepatocytes	cell culture	1×10^{-4} M	--	--	NC	Williams, 1978
Sister chromatid exchange	Chinese hamster pseudodiploid cells	cell culture	1×10^{-4} M	--	+	no decrease in mitotic index	Abe and Sasaki, 1977
Sister chromatid exchange	Chinese hamster pseudodiploid cells	cell culture	2×10^{-4} M	--	-	no decrease in mitotic index	Abe and Sasaki, 1977
Sister chromatid exchange	Chinese hamster pseudodiploid cells	cell culture	5×10^{-4} M	--	+	no decrease in mitotic index	Abe and Sasaki, 1977
Sister chromatid exchange	Chinese hamster pseudodiploid cells	cell culture	1×10^{-3} M	--	+	significant decrease in mitotic index	Abe and Sasaki, 1977

NC = No comment

the study of Abe and Sasaki (1977). Although these investigators reported the induction of sister chromatid exchange in Chinese hamster cells with biphenyl, a dose/response relationship was not found.

5.3. TERATOGENICITY

Khera et al. (1979) administered by gavage 10 mL of corn oil suspensions containing 0, 125, 250, 500 or 1000 mg biphenyl/kg to groups of 20 pregnant Wistar rats on days 6-15 of gestation. Day 1 of gestation was the day on which a sperm-positive vaginal smear was observed. Dams were weighed and killed on the 22nd day of gestation, whereupon the uterine contents were removed. Fetuses were examined for viability and internal and external anomalies, and the number of copora leutea were determined. The carcasses of the dams underwent necropsy. No maternal or fetal evidence of toxicity at the dose levels 125, 250 or 500 mg/kg was observed when compared with the control group. The group receiving 1000 mg/kg had some evidence of fetotoxicity (reduced fetal weight, reduced number of live fetuses and increased resorptions), but these values were not significantly different from controls. Increased maternal mortality (5/20) was observed at this dose level.

5.4. OTHER REPRODUCTIVE EFFECTS

Ambrose et al. (1960) conducted two reproduction studies with albino rats wherein weanling or 90-day-old rats were given diets containing 0, 0.1 or 0.5% biphenyl. Groups of ten female and 5 male weanling rats were fed 0 or 0.1% biphenyl in the diet for 60 days before mating. The diets were continued through weaning of the offspring. Nine female and 3 male rats were kept on a similar regimen, except that they were given a diet containing 0.5% biphenyl. Similar groups of 90-day-old rats were given 0, 0.1 or

0.5% biphenyl diets for 11 days and were then mated. The diets were continued through weaning of the offspring. No significant effects of biphenyl treatment on the number of rats giving birth, the total number of pups born or litter size were observed. No other observations were reported except that the results were in accord with a previous study by Stanford Research Institute (n.d.).

A similar study by Stanford Research Institute (SRI, n.d.) was reviewed by Ambrose et al. (1960) and was not located in searches of the published literature. In this three-generation study, 0.01 and 0.1% dietary biphenyl had no effects on reproduction in rats, but 1.0% dietary biphenyl produced (unspecified) adverse effects.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Ambrose et al. (1960) gave groups of 15 male and 18 female weanling albino rats diets containing 0, 0.001, 0.005, 0.01, 0.05, 0.10, 0.50 or 1.0% biphenyl for 700 days. Growth, food consumption and hemoglobin were monitored at intervals throughout treatment. Gross and microscopic histopathologic evaluation was performed after treatment. Growth retardation, reduced hemoglobin levels and decreased food intake were observed in rats fed diets containing 1.0 and 0.5% biphenyl, but not at lower dietary levels. All rats maintained on 1.0 or 0.5% dietary biphenyl had evidence of kidney damage, including irregular scarring, lymphocytic infiltration, tubular atrophy and patchy tubular dilation. Renal effects in most of the rats fed lower dietary levels of biphenyl were not different from controls. However, 2 male rats receiving 0.1 or 0.05% biphenyl in the diet had disintegrated blood cells in the renal pelvis and 2 other males receiving 0.1 or 0.05% had small basophilic concretions in the medullas of the kidney. Blood was observed in the renal pelvis in one animal from each of the groups given 0.01, 0.005,

0.001 and 0% biphenyl in the diet. The authors concluded that the histopathologic changes in the kidneys of rats fed <0.1% biphenyl in the diet were not treatment-related. Results of another study from the same laboratory (Booth et al., 1961) indicated that the renal damage seen at >0.5% dietary biphenyl could be reversed by placing the animals on a control diet.

An apparently unpublished study by Stanford Research Institute (SRI, n.d.) was reviewed by Ambrose et al. (1960). In this study, rats given 0.01, 0.03 or 0.1% biphenyl in the diet for 3 months were not significantly different from controls as measured by growth, food efficiency, organ weights, histologic appearance of tissues or blood urea nitrogen values. A long-term feeding study with rats, also by Stanford Research Institute (SRI, n.d.) was confounded by a severe respiratory infection that caused high mortality among controls. In addition, many of the treated and control rats had tubular dilation of the kidneys of various degrees of severity. The sporadic nature of the findings apparently precluded the assignment of no-effect and effect levels of exposure. Stanford Research Institute performed long-term feeding studies with monkeys as well as with rats. Monkeys receiving 0.01 or 1.0% dietary biphenyl for 1 year had no effects, while those receiving 1.0% dietary biphenyl for 1 year had no gross or histologic effects other than an increase in the liver weight.

Deichmann et al. (1947) conducted a subchronic inhalation study of biphenyl impregnated celite dust in rats, rabbits and mice. Three albino rabbits and 10 SD rats were exposed to dust containing 300 mg biphenyl/m^3 7 hours/day, 5 days/week over 90 days. Three rabbits and six rats were similarly exposed to 40 mg biphenyl/m^3 for 64 days. Four rats and 12 mice were similarly exposed to 5 mg biphenyl/m^3 for 87 days. Controls were not reported. All animals had "severe bronchopulmonary lesions" including

emphysema, lobular pneumonia, bronchitis and multiple abscesses of the lungs. Minor liver and kidney damage was also observed. Since dust controls were not used, the pulmonary effects cannot be ascribed solely to the biphenyl in the dust.

5.6. OTHER RELEVANT INFORMATION

Acute exposure to high levels of biphenyl appears to cause eye and skin irritation, hepatotoxicity, renal toxicity and toxic effects on the central and peripheral nervous systems (Sandmeyer, 1981). The Registry of Toxic Effects of Chemical Substances lists the following LD_{50} values:

rat - oral - 3280 mg/kg
mouse - intravenous - 56 mg/kg
rabbit - oral - 2410 mg/kg

Sondergaard and Blom (1979) performed 21-day feeding studies to assess the effect of diet on the induction of polycystic renal lesions in the rat by biphenyl. The lesions were similar to those reported by Ambrose et al. (1960) in chronic studies (see Section 5.5.). Groups of 8-10-week-old male and female Wistar rats (usually 10/sex/dose level) were fed biphenyl in commercial rat chow in a semisynthetic diet. In rats fed the commer- cial chow, the no-effect level for renal effects was 300 mg biphenyl/kg bw/day; kidney weight, urine volume and urine specific gravity were increased at an intake of >500 mg/kg bw/day, and polycystic renal changes occurred at 1000 mg/kg bw/day. In rats fed the semisyn- thetic diet, an increase in relative kidney weight occurred at the lowest intake tested, 50 mg biphenyl/kg bw/day; increased relative kidney weight, polycystic changes and increased urine volume and specific gravity were seen at >150 mg/kg bw/day. (According to the authors, the intake of 50 mg/kg bw/day resulted from a concentration of 0.5% biphenyl in the semisyn- thetic diet).

A study investigating the death of a biphenyl paper maker was reported by Hakkinen et al. (1973). Death occurred after the man who had been exposed to biphenyl (4.4-128 mg/m^3) on ~100 days/year for 11 years. The cause of death was acute yellow liver atrophy. Eight co-workers had evidence of hepatic and nervous system toxicity.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute toxicity of biphenyl was determined for several fish species and daphnids (Dill et al., 1982). The 96-hour LC_{50} values for rainbow trout, Salmo gairdneri, bluegill sunfish, Lepomis macrochirus, and sheepshead minnows, Cyprinodon variegatus, were determined to be 1.5, 4.7 and 4.6 mg/ℓ respectively. The 96-hour LC_{50} for fathead minnows, Pimephales promelas, was 6 mg/ℓ near the water solubility of biphenyl. The 48-hour static LC_{50} for Daphnia magna was 2.1 mg/ℓ. LeBlanc (1980) reported static 24 and 48-hour LC_{50} values for D. magna to be 27.0 and 4.7 mg/ℓ, respectively. The concentration of biphenyl that had no discernible effect on the daphnids was reported to be <2.2 mg/ℓ.

6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic exposure to biphenyl on aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

The effects of biphenyl on the growth of a blue-green alga, Agmenellum quadruplicatum, and a green alga, Chlorella autotrophica, was tested by plate zone of inhibition tests (Pulich et al., 1974). For A. quadruplicatum, 10 mg biphenyl/plate caused complete growth inhibition (36 mm zone of inhibition), while at 2.0, 1.0 and 0.5 mg/plate, the zone of inhibition was 21, 4 and 0 mm, respectively. Similarly, biphenyl applied at 2.0 and 1.0 mg/plate caused 10 and 5 mm zones of inhibition, respectively, in C. autotrophica (Pulich et al., 1974).

6.4. RESIDUES

Clement et al. (1980) reported that bivalves, Macoma balthica, exposed to crude oil in the water accumulated biphenyls up to 1.5 µg/g wet weight

tissue. Oysters, Crassostrea virginica, accumulated 0.2 µg biphenyl/g wet weight tissue after exposure to 1% aqueous fuel oil for 4 days (Neff, 1975; Neff et al., 1976). Within 8 hours of exposure to a concentrated oil-water dispersion, oysters and clams, Rangia cuneata, accumulated 0.3 and 0.1 µg/g wet weight tissue, respectively (Neff, 1975; Neff et al., 1976).

Kveseth et al. (1982) reported biphenyl levels of 26 ng/l in effluent from the Bekkelaget, Norway, Sewage Treatment Plant. Samples of tap water from Helsinki, Finland, Horsholm, Denmark, Uppsala, Sweden, and Oslo, Norway, contained biphenyl at 4.8, 2.2, 0.78 and 0.26 ng/l, respectively (Kveseth et al., 1982).

The bioaccumulation factor of biphenyl in Chlorella fusca (var. vacuolata) exposed to 50 µg/l for 24 hours was determined to be 540 (Geyer et al., 1981).

6.5. OTHER RELEVANT INFORMATION

The metabolic derivatives of biphenyl in the crustacean, Cirolana borealis, were reported as 2-hydroxybiphenyl [64.1% (of the total biphenyl or biphenyl metabolites encountered in the organism and its environment) in tissue; 10.3% in seawater], 4-hydroxybiphenyl (12.8% in seawater) and 4,4-dihydroxybiphenyl (12.8% in seawater) (Meyer and Bakke, 1977). In the gastropod mollusk, Buccinum undatum, unchanged biphenyl (26.5% of total biphenyl and metabolites encountered) and 2-hydroxybiphenyl (44.9%) were detected in the animal while sea water contained 2-hydroxy(16.3%) and 4-hydroxybiphenyl (12.3%). The echinoderm, Ophiocomina nigra, contained 2-hydroxybiphenyl (27.8% of total biphenyl and metabolites encountered), biphenyl (4.1%), 4-hydroxy(4.1%) and 4,4'-dihydroxy-derivatives (5.6%). The ambient seawater surrounding O. nigra contained biphenyl (26.4%), 2-hydroxy (26.4%) and 4-hydroxybiphenyl (5.6%) (Meyer and Bakke, 1977).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

According to the Occupational Safety and Health Administration (OSHA) standard for biphenyl in workplace air requires that the concentration not exceed 0.2 ppm on an 8-hour TWA basis (Code of Federal Regulation, 1981). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a 0.2 ppm concentration limit for an 8-hour TWA and a 0.6 ppm Short Term Exposure Limit (STEL) (ACGIH, 1980).

Tolerances for biphenyl residues on citrus fruit are 110 ppm in the United States and 70 ppm in Europe and Japan (Wardowski et al., 1979). An ADI of 0.05 mg/kg/day for man has been estimated by the World Health Organization (Isshiki et al., 1982).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of biphenyl were not located in the available literature.

B. RISK ASSESSMENT

In the absence of data implicating biphenyl as a carcinogen (BRL, 1968; Ambrose et al., 1960), mutagen or teratogen, reliance must be placed on the chronic toxicity study of Ambrose et al. (1960) for the assessment of human risk from biphenyl exposure. This study is useful because eight different dietary dosage levels were administered to groups of 15 male and 15 female rats for a sufficient portion of their lifetime (i.e., ~2 years). A NOAEL of 0.1% dietary biphenyl was identified. Dietary levels of >0.5% biphenyl were associated with kidney damage, reduced hemoglobin levels, decreased food intake and growth and decreased longevity. The NOAEL of 0.1% dietary biphenyl is equivalent to 50 mg biphenyl/kg bw/day, assuming that rats consume food at a rate of 5% of their bw/day. An ADI of 0.5 mg/kg/day (or 35 mg/day for a 70 kg man) is obtained by dividing 50 mg/kg/day by an uncertainty factor of 100. This factor is applied to extrapolate from a chronic animal study to humans. Because of uncertainties regarding the threshold for renal damage in the Ambrose et al. (1960) study (one animal in each of the lower dose groups including the control groups had detectable blood in the renal pelvis), an uncertainty factor of 1000 might be more appropriate and would result in an ADI of 0.05 mg/kg/day or 3.5 mg/day for a 70 kg man.

9. REFERENCES

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

Most of these searches were conducted in June, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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